Use of human iPS cells to study spinal muscular atrophy

Grant Award Details

Use of human iPS cells to study spinal muscular atrophy

Grant Type: Basic Biology III

Grant Number: RB3-02161

Project Objective: To characterize disease phenotypes in SMA iPS cell-derived MNs

Investigator:

Name:	Jiing-Kuan Yee
Institution:	City of Hope, Beckman Research Institute
Type:	PI

Disease Focus: Neurological Disorders, Pediatrics, Spinal Muscular Atrophy

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,268,868

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3/NCE

View Report

Grant Application Details

Application Title: Use of human iPS cells to study spinal muscular atrophy

Public Abstract: Spinal muscular atrophy (SMA) is one of the most common autosomal recessive disorders that cause infant mortality. SMA is caused by loss of the Survival of Motor Neuron (SMN) protein, resulting in motor neuron (MN) degeneration in the spinal cord. Although SMN protein plays diverse roles in RNA metabolism and is expressed in all cells, it is unclear why a deficiency in SMN only causes MN degeneration. Since patient samples are rarely available, most knowledge in SMA is gained from animal model studies. While these studies have provided important information concerning the cause and mechanism of SMA, they are limited by complicated genetic manipulation. Results from different models are also not always consistent. These problems can be resolved if SMA patient's MNs become readily available. Recent progress in the generation of induced pluripotent stem (iPS) cells from differentiated adult cells provides an opportunity to establish human cell-based models for neurodegenerative diseases. These cells, due to their self-renewal property, can provide an unlimited supply of the affected cell type for disease study in vitro. In this regard, SMA iPS cells may represent an ideal candidate for disease modeling as SMA is an early onset monogenic disease: the likelihood to generate disease-specific phenotypes is therefore higher than iPS cells derived from a late onset disease. In addition, the affected cell type, namely MNs, can readily be generated from iPS cells for the study. For these reasons, we established several SMA iPS cell lines from a type 1 patient and showed specific deficits in MNs derived from these iPS cells. Whether MNs derived from these iPS cell lines can recapitulate a whole spectrum of SMA pathology in animals and patients remains unclear. An answer to this question can ensure the suitability of using the iPS cell approach to study SMA pathogenesis in cell culture. We propose to examine cellular and functional deficits in MNs derived from these SMA iPS cells in Aim 1. The availability of these iPS cells also provides an opportunity to explore the mechanisms of selective MN degeneration in SMA. Dysregulation of some cellular genes has been implicated in SMA pathogenesis. We propose to use these iPS cell lines to address how one such gene is affected by SMN deficiency (Aim 2) and how a deficit in these genes leads to selective MN degeneration (Aim 3). Our study should provide valuable insights in the understanding of SMA pathogenesis and aid in exploring new molecular targets for drug intervention.

Statement of Benefit to California: Spinal muscular atrophy (SMA) is one of the most common autosomal recessive disorders in humans and the most common genetic cause of infant mortality. SMA is caused by loss of the Survival of Motor Neuron (SMN) protein, resulting in motor neuron (MN) degeneration in the spinal cord. SMA has a carrier frequency of approximately 1 in 35 and an incidence of 1 in 6000 in human population. In severe SMA cases, the disease onset initiates before 6 months of age and death within the first 2 years of life. Currently, there is no cure for SMA. Since MN samples from patients are rarely available, most knowledge in SMA is gained from animal model studies. While these studies have provided important information concerning the cause and mechanism of SMA, they are limited by complicated genetic manipulation. Results from different models are not always consistent either. Large-scale drug screening to treat SMA is also hampered by the lack of suitable cell lines for the study. These problems can potentially be resolved if SMA patient's MNs become readily available. Our effort to derive induced pluripotent stem (iPS) cells from a SMA patient provides an unlimited supply of SMA cells to carry out studies to explore the disease mechanism in vitro. A better understanding in the disease mechanisms would benefit California by the identification of potential cellular targets for drug treatment. The knowledge gained from our study can also facilitate the use of these iPS cells as a platform for large-scale drug screening and validation. Our study should provide valuable insights in the understanding of SMA pathogenesis and aid in exploring new molecular targets for drug intervention.